PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Adverse events and overall health and wellbeing after COVID-19 vaccination: interim results from the VAC4COVID cohort safety study
AUTHORS	Rogers, Amy; Rooke, Evelien; Morant, Steve; Guthrie, Greg; Doney, Alex; Duncan, Andrew; Mackenzie, Isla; Barr, Rebecca; Pigazzani, Filippo; Zutis, Krists; MacDonald, Thomas M.

VERSION 1 – REVIEW

REVIEWER	Boekel, Laura Amsterdam Rheumatology and Immunology Center, Rheumatology
REVIEW RETURNED	03-Mar-2022

GENERAL COMMENTS	The study of Rogers and colleagues describes the occurrence of adverse events after COVID-19 vaccinations and phycological consequences of these vaccinations in a large cohort of British people of the general population. I think the data are interesting, especially data on effects of vaccination on menstrual changes, as this has been repeatedly reported in the media; the results of Rogers and colleagues provide reassuring data on this topic. However, I do have some major concerns regarding the reported incidence of adverse events and the possible amount of missing data in the study (see comments below), that I think should be addressed before publication of the results. General comments: - The first study outcome that is described in the result section is “medical adverse events”. However, this outcome is not described in the objective section nor the outcome section in the methods. In addition, the sequence of outcomes described in the objective section, outcome section, statistical analyses section and results section is not consisted. To improve the clarity of the manuscript, I recommend to be consistent in the order in which the outcomes are described. Abstract: - The objective described in the abstract is to report “health and wellbeing” after COVID-19 vaccination. However, in the method section of the main text, this is described as incidence of short-term reactogenicity, menstrual changes, and health and wellbeing. This is more specific and clear, and as the main focus of the manuscript seems to be the occurrence of adverse events, I recommend to specifically describe this in the objectives of the abstract as well. - In line with the previous comment, when I first read the title of the manuscript, I did not expect to read an article that reported

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	adverse events (I expected to read an article which main focus would be psychological consequences of COVID-19 vaccination, or physical consequences in general). I recommend to consider to specifically mention adverse events in the title of the manuscript. - In Results of the abstract, it is stated that “a small proportion of women reported menstrual symptoms”. I recommend to report the exact proportion as described in the main text as well. Methods: - Participants: in the introduction section it is described that adverse events can be validated, but it remains unclear how this is (or can be) done. On the website I read that participants are asked to report their GP, and to report enough personal information to be able to track them in health codes. I recommend to add this information to the manuscript. - Variables: people who report medical adverse events are also asked to rate the severity of this adverse event (mild, moderate or severe). What is the definition or description that is used for mild, moderate and severe? To my knowledge, ‘mild’ is generally defined as “awareness of symptom, but easily tolerated”, so if this is the case, how can medical adverse events (in the manuscript defined as significant changes in health and wellbeing; disruptive in usual activities) be mild? It seems as if people who report mild medical adverse events are included in the total percentage of people that report medical adverse events, but perhaps they should be excluded from the overall proportion (as the adverse event is not severe enough to fulfill the definition of medical adverse event). - In the objectives it is described that the study aims to investigate short-term reactogenicity. However, in the results section it becomes clear that reactogenicity is measured during the whole follow-up time of the study, and thus up to 200 days after vaccination, which does not seem ‘short-term’ to me. Please rephrase the description in the method section. - Related to the previous comments, to my knowledge, reactogenicity related adverse events are per definition short term. It is therefore questionable that reactogenicity related adverse events such as muscle and joint pain are still related to the vaccination when it is reported 120 days after the vaccination. Figure 2 that shows the cumulative events up to 200 days after vaccination might therefore have a limited additional value compared to only showing the proportions during the first 7 or 14 days after vaccination (unless this figure shows the incidence of AE’s during the first seven days, and the time since vaccination indicates the time at which it is reported in the questionnaire rather than the time at which the adverse event occurred, if this is the case it should be described more clearly). - As I understand, all participants are invited to complete questionnaires on adverse events at specific timepoints after vaccination (every week in the first months, and then monthly), and everyone who completed at least 1 FU questionnaire has been included for analyses. This must have led to a considerable amount of missing data on each timepoint, so how were these missings handled? In addition, how were people asked to report on their adverse event; e.g. if the first FU questionnaire that a person completes is the one that is sent 4 weeks after vaccination, does that person still report adverse events during the first 7 days? And related to this, how are people “censored” in Figure 1 and when do people contribute to “at risk”; if someone completed only the questionnaire sent after 4 weeks, are they at risk during the

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	time before that? I recommend to add data on the number of people that completed the solicited questionnaires at each timepoint, to get more insight into the amount of missing data. It would also be insightful to provide data on the number of adverse events that were reported via spontaneous completion of questionnaires, and how this compares with the proportion of adverse events reported via the solicited questionnaires. - In Figure 1, the pink and purple lines overlap a lot, which makes it hard to see that it shows two different curves. I recommend to use a different order in the colors, so that pink and purple don't overlap (more contrast in color between these two lines should improve the clarity of each line). - Why was 65 years used as cut-off age for menstruation changes? The date of last menstruation was assessed, so why not include only pre-menopausal women? - In Figure S3 the lines of the cumulative events cross at several points, but cox regression was used to quantify the relationship. Did you test whether the proportional hazard assumption was met? If so, I recommend to describe this in the method section. Results: - The study observed incidences of reactogenicity related adverse events ranging between 1.6-7.8% during the first seven days. This proportion seems very low to me, as most studies report proportions over 70-80%. In the introduction section it is even mentioned that most side effects are likely underreported, and that the present study allows a more accurate estimation of adverse event rates. Do you have an explanation for these low adverse event rates? Is this for example because of missings? - Related to the previous comment, the incidence of medical adverse events (which are mostly more severe compared to reactogenicity related adverse events) is higher than the incidence of reactogenicity related adverse events; 89% did not report medical AE's, so 11% did. One would expect the incidence of more severe adverse events to be (much) lower than the incidence of reactogenicity related adverse events. Do you have an explanation for these results? - Are reasons for hospitalization assessed? Discussion: - In the first paragraph of the discussion section, it is stated that reactogenicity-related symptoms are comparable to those associated with seasonal influenza vaccinations. However, the study that is used as reference (19) specifically assessed moderate/severe adverse events, whereas the present study also included mild adverse events. Are there other studies on adverse events after influenza vaccines that also assessed mild adverse events? If so, I recommend to choose such studies as reference instead, as these study designs are more comparable to the present study. - It is mentioned that proportions of severe AE's increase with time, but when looking at table 2, the proportions of severe adverse events and hospitalizations seems to be quite constant over time. So on what data is this statement based? I recommend to describe these results more clearly in the results section if you choose to point this out in the discussion section. - It is described that the time-to-event analyses accounts for confounding by indication. Could you explain this? - The amount of missing data seems quite high (although it is not yet clearly described). I think this is an important limitation of the

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	study, as it limits the accuracy and validity of estimated adverse events rates at specific timepoints. This should be more clearly described as a limitation.

REVIEWER	Thurin, Nicolas Université de Bordeaux, Bordeaux PharmacoEpi
REVIEW RETURNED	09-Mar-2022

GENERAL COMMENTS	The authors set up a prospective cohort of UK residents who have received or may receive a UK-approved vaccines for COVID-19 disease. The active monitoring of potential vaccine safety outcomes (and wellbeing) is conducted through a website where participants receive scheduled questionnaires and can also self-report outcomes. The manuscript is well written; however, some points of method could be clarified to facilitate understanding. Some choices would also need to be more widely developed, especially the way changes in patient health are collected. # Major comments 1) The definition of the index date, i.e., the start of follow-up time, lacks of clarity. On reading of the section Statistical Analysis, once can expect that each vaccine dose is considered separately. However, when looking at Table 1, this does not seem to be the case. This is particularly troublesome for variables such as “Had COVID before vaccination” since this status can change between the two doses. 2) From what I have understand, a “yes” answer to the following question was require to allow participants to enter adverse medical event: "Have there been any significant changes in your health and wellbeing for any reason (including any that you think may have been due to COVID-19 vaccination)? By 'significant', we mean that it was disruptive of usual activities, caused loss of work or education days, or led to hospitalisation." This question and the definition of “significant” have potentially led participant to under-report mild/moderate reactogenicity-related adverse event such as headache, fatigue, muscle or joint pain, fever, nausea, dizziness, or local vaccine reaction, i.e., the main outcome measures. The event rate observed in a similar study recently published (near 63% of patient with reactogenicity outcome post vaccination, https://doi.org/10.1016/j.vaccine.2022.01.013), which is significantly higher than the one reported here (1.3%-7.8%), is consistent with this observation. This point should be discussed, as well as its impact on the interpretation possible of Table 2 (are Mild reaction really Mild since they are “significant”?) 3) Bringing information on improvement of health / wellbeing in vaccine assessment is a good idea. However, an indicator on wellbeing deterioration could also have been beneficial, especially in the frame of a PASS. Combined with the previous comment, the absence of these indicator may give the impression that these questions are biased, and feed vaccine skepticism. I would recommend to justify this choice. # Minor comments

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	1) It takes some time to understand that patients may either register before or after vaccination. This point should be made clear in the method/participants section. 2) There are no exclusion criteria relative to the time to enroll after vaccination administration. This aspect may expose data collection to recall bias and also potentially to the over-registration of participant that experimented an outcome. If space allows, this point could be shortly discussed. 3) Description around how vaccine exposure is captured (batch, dates…) could be moved to the "Exposure" section. 4) Text elaborating around Table 1 would be appreciated. A clear definition of the index date will help to better understand the content of the different categories.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Comment:

The first study outcome that is described in the result section is "medical adverse events".However, this outcome is not described in the objective section nor the outcome section in the methods. In addition, the sequence of outcomes described in the objective section, outcome section, statistical analyses section and results section is not consisted. To improve the clarity of the manuscript, I recommend to be consistent in the order in which the outcomes are described.

Response:

Thank you for pointing out this inconsistency. The order in which outcomes are described has been standardised in all sections as follows:

"Main outcome measures - The outcomes reported in this interim analysis include: individual adverse events (including hospitalisations), reactogenicity-type adverse events (defined as headache, fatigue, muscle or joint pain, fever, nausea, dizziness, or local vaccine reaction), menstrual changes, and reported improvement in overall health and wellbeing."
Comment:
The objective described in the abstract is to report "health and wellbeing" after COVID-19 vaccination. However, in the method section of the main text, this is described as incidence of short-term reactogenicity, menstrual changes, and health and wellbeing. This is more specific and clear, and as the main focus of the manuscript seems to be the occurrence of adverse events, I recommend to specifically describe this in the objectives of the abstract as well.

Response:

The abstract has been updated as above (Main outcome measures) and as follows:

"Objectives - To describe the incidence of adverse events, reactogenicity symptoms, menstrual changes, and overall self-rated improvement in health and wellbeing after COVID-19 vaccination."

Comment:

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In line with the previous comment, when I first read the title of the manuscript, I did not expect to read an article that reported adverse events (I expected to read an article which main focus would be psychological consequences of COVID-19 vaccination, or physical consequences in general). I recommend to consider to specifically mention adverse events in the title of the manuscript.

Response:

We have amended the title as follows:

“Adverse events and overall health and wellbeing after COVID-19 vaccination: interim results from the VAC4COVID cohort safety study”

Comment:

In Results of the abstract, it is stated that “a small proportion of women reported menstrual symptoms”. I recommend to report the exact proportion as described in the main text as well.

Response:

This sentence has been amended to include the proportion:

“0.3% of women reported menstrual symptoms after vaccination; no differences between vaccine type or dose order were detected.”

Comment:

Participants: in the introduction section it is described that adverse events can be validated, but it remains unclear how this is (or can be) done. On the website I read that participants are asked to report their GP, and to report enough personal information to be able to track them in health codes.I recommend to add this information to the manuscript.

Response:

A short description of the clinical event validation process has been added to the Methods section:

“We present only unvalidated data in this interim analysis. However, the VAC4COVID study design does allow for clinical validation of potential AESIs. Briefly, this is done as follows: potential AESIs are identified using pre-determined MedDRA® code searches and manual clinical review of reported events. The study team then obtain additional supporting information (e.g. description of events, hospital discharge letter, test results) directly from the participant (where appropriate) and their registered GP. These additional supporting data are reviewed independently by two clinicians to determine whether the event meets existing AESI clinical definitions. Disagreements are resolved by consensus with a third clinician.”

Comment:

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Variables: people who report medical adverse events are also asked to rate the severity of this adverse event (mild, moderate or severe). What is the definition or description that is used for mild,moderate and severe? To my knowledge, 'mild' is generally defined as "awareness of symptom, buteasily tolerated", so if this is the case, how can medical adverse events (in the manuscript defined assignificant changes in health and wellbeing; disruptive in usual activities) be mild? It seems as if people who report mild medical adverse events are included in the total percentage of people that report medical adverse events, but perhaps they should be excluded from the overall proportion (as the adverse event is not severe enough to fulfill the definition of medical adverse event).

Response:

We have amended the Methods section, as follows, to clarify the guidance given to participants on self-rating severity:

"Participants are asked to enter the date of onset, if they were hospitalised, and subjective estimation of event severity for each event reported using the MedDRA®-based look-up. Severity assessment permits three levels of severity (mild, moderate, severe) with no additional guidance on criteria for severity selection."

We have also added a section to the discussion to address the disparity between participant-reported severity and the limits on severity imposed by the guidance text on entering events that have disrupted usual activities.:

"By defining an adverse event as a significant change in health and wellbeing in the online questionnaire (e.g. disruptive of usual activities), all events included in this analysis would likely be at least moderate according to severity grading scales commonly used in clinical research. In addition, the open question format did not prompt specific symptoms, which may reduce reporting of events that individual participants did not consider important or relevant. Therefore, we expect the rate of adverse events reported by our participants as mild to be lower than those reported in studies that did not use the same question format. For example, a Dutch web-based cohort study reporting data up to 13 days after vaccination asked participants to indicate if they had experienced specific common vaccine adverse reactions[13]. The Dutch study reported a far higher 62.9% overall rate of reactogenicity adverse events, similar to phase 3 vaccine trial findings."

Comment:

In the objectives it is described that the study aims to investigate short-term reactogenicity.However, in the results section it becomes clear that reactogenicity is measured during the whole follow-up time of the study, and thus up to 200 days after vaccination, which does not seem 'short-term' to me. Please rephrase the description in the method section.

Response:

The phrase "short-term" has been removed and "reactogenicity-type" used throughout, in recognition that these symptoms are unlikely to be due to vaccine reaction when occuring after 7 days.

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Comment:

Related to the previous comments, to my knowledge, reactogenicity related adverse events are per definition short term. It is therefore questionable that reactogenicity related adverse events such as muscle and joint pain are still related to the vaccination when it is reported 120 days after thevaccination. Figure 2 that shows the cumulative events up to 200 days after vaccination might therefore have a limited additional value compared to only showing the proportions during the first 7or 14 days after vaccination (unless this figure shows the incidence of AE's during the first seven days, and the time since vaccination indicates the time at which it is reported in the questionnaire rather than the time at which the adverse event occurred, if this is the case it should be described more clearly).

Response:

The K-M curves in Fig 1 show that most reactogenicity events do indeed occur in the first week and accumulate very slowly thereafter. That is why, for Fig 2, we have extracted rates at day 7 post vaccination to compare vaccines. Day seven is specified in both the title and x-axis label of Fig 2.

Comment:

As I understand, all participants are invited to complete questionnaires on adverse events at specific timepoints after vaccination (every week in the first months, and then monthly), and everyone who completed at least 1 FU questionnaire has been included for analyses. This must have led to a considerable amount of missing data on each timepoint, so how were these missings handled? In addition, how were people asked to report on their adverse event; e.g. if the first FU questionnaire that a person completes is the one that is sent 4 weeks after vaccination, does that person still report adverse events during the first 7 days? And related to this, how are people"censored" in Figure 1 and when do people contribute to "at risk"; if someone completed only thequestionnaire sent after 4 weeks, are they at risk during the time before that? I recommend to add data on the number of people that completed the solicited questionnaires at each timepoint, to get more insight into the amount of missing data. It would also be insightful to provide data on the number of adverse events that were reported via spontaneous completion of questionnaires, and how this compares with the proportion of adverse events reported via the solicited questionnaires.

Response:

We chose to use a time-to-event analysis because in such analyses the absence of negative reports does not matter. Our assumption was that when events do occur, patients are likely to report them. The calculation of time to first positive report is not affected by the absence of negative reports at an earlier date.

The censorship rules for the time-to-event analysis are already stated in the statistical analysis section of Methods. For clarity, we have restated the at-risk period in legend of Figure 1:

"Figure 1: Kaplan-Meier curves for any reactogenicity-related symptom. Individuals considered "at-risk" from date of vaccination until last submitted follow-up."

We have added the following sentence to the

We have also included missing data as possible source of bias in the Discussion section:

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"…participant-reported events may be more susceptible to missing data and misclassification. With the assumption that missing data would be more likely in participants who had not experienced an adverse event, given that participants were encouraged to record events at any time during the study, we mitigated the potential impact of missing data by using a time-to-event rather than cross-sectional approach. However, there will likely be a degree of missingness in adverse event data, leading to underestimating true event rates and possible bias."

Comment:

In Figure 1, the pink and purple lines overlap a lot, which makes it hard to see that it shows twodifferent curves. I recommend to use a different order in the colors, so that pink and purple don't overlap (more contrast in color between these two lines should improve the clarity of each line).

Response:

A new Figure 1 with higher contrast colours has been provided.

Comment:

Why was 65 years used as cut-off age for menstruation changes? The date of last menstruation was assessed, so why not include only pre-menopausal women?

Response:

This was a typographical error in the results section. The correct age range used in the analysis was 18-59. This has been corrected in the text and figure, accordingly. The upper cut-off of 59 was chosen as it is the mean UK menopause age (UK Biobank estimate) + 2SD. Last mentrual period data is only collected from participants who report a pregnancy at baseline or during the study.

Comment:

In Figure S3 the lines of the cumulative events cross at several points, but cox regression wasused to quantify the relationship. Did you test whether the proportional hazard assumption was met?If so, I recommend to describe this in the method section.

Response:

Yes, the proportional hazards assumption was met. The following text has beed added to the Statistical Analysis Section:

"proportional hazard assumption met, p=0.73"

Comment:

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The study observed incidences of reactogenicity related adverse events ranging between 1.6-7.8% during the first seven days. This proportion seems very low to me, as most studies report proportions over 70-80%. In the introduction section it is even mentioned that most side effects are likely under reported, and that the present study allows a more accurate estimation of adverse event rates. Do you have an explanation for these low adverse event rates? Is this for example because of missings?

Response:

As responded to above, we have amended the Discussion section to address two potential sources of this lower incidence rate: the questions used to elicit reports of adverse events, and, potential missingness.

Comment:

Related to the previous comment, the incidence of medical adverse events (which are mostly more severe compared to reactogenicity related adverse events) is higher than the incidence of reactogenicity related adverse events; 89% did not report medical AE's, so 11% did. One would expect the incidence of more severe adverse events to be (much) lower than the incidence of reactogenicity related adverse events. Do you have an explanation for these results?

Response:

All reported events were at least moderate severity due to the wording of the questionnaire (secondary participant-assessed severity, notwithstanding). The reactigenicity-type symptoms were a subset of these. We did not collect data on reactogenicity-type symptoms that did not meet the definition of AE. Terminology has been adjusted throughout with additional clarification on severity in methods and discussion of the limnitations of this approach.

Comment:

Are reasons for hospitalization assessed?

Response:

We do collect this data and use it for identification of SAEs and AESIs in the full study. These data were was not assessed in this analysis. Headings on Table 2 have been adjusted for clarity and "Reasons for hospitalisation were not assessed in this analysis." added to Outcomes.

Comment:

In the first paragraph of the discussion section, it is stated that reactogenicity-related symptoms are comparable to those associated with seasonal influenza vaccinations. However, the study that is used as reference (19) specifically assessed moderate/severe adverse events, whereas the present study also included mild adverse events. Are there other studies on adverse events after influenza vaccines that also assessed mild adverse events? If so, I recommend to choose such studies as reference instead, as these study designs are more comparable to the present study.

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Response:

Please see updated Discussion section above regarding event severity and comparison with a Dutch study using study design but different question format.

Comment:

It is mentioned that proportions of severe AE's increase with time, but when looking at table 2,the proportions of severe adverse events and hospitalizations seems to be quite constant over time. So on what data is this statement based? I recommend to describe these results more clearly in the results section if you choose to point this out in the discussion section.

Response:

Thank you for pointing out this error. The statement has been removed.

Comment:

It is described that the time-to-event analyses accounts for confounding by indication. Could you explain this?

Response:

This was an error. The survival analysis was not done using a proportional hazards model. The Discussion text has been adjusted accordingly.

"Evolving UK vaccine deployment policies have resulted in differences in the characteristics of participants receiving each vaccine type (including age and co-morbidity); this may introduce confounding. For example, health and social care workers are likely to have different vaccination and COVID-19 exposure patterns than the general population."

Comment:

The amount of missing data seems quite high (although it is not yet clearly described). I think this is an important limitation of the study, as it limits the accuracy and validity of estimated adverse events rates at specific timepoints. This should be more clearly described as a limitation.

Response:

As above, this has been addressed in the discussion.

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Reviewer 2

Comment:

The definition of the index date, i.e., the start of follow-up time, lacks of clarity. On reading of the section Statistical Analysis, once can expect that each vaccine dose is considered separately. However, when looking at Table 1, this does not seem to be the case. This is particularly troublesome for variables such as “Had COVID before vaccination” since this status can change between the two doses.

Response:

The data presented in column one of Table 1 are baseline variables. The "had COVID before" refers to baseline covid status at study entry. The table has been updated for clarity.

Comment:

From what I have understand, a “yes” answer to the following question was require to allow participants to enter adverse medical event: "Have there been any significant changes in your health and wellbeing for any reason (including any that you think may have been due to COVID-19 vaccination)? By 'significant', we mean that it was disruptive of usual activities, caused loss of work or education days, or led to hospitalisation." This question and the definition of “significant” have potentially led participant to under-report mild/moderate reactogenicity-related adverse event such as headache, fatigue, muscle or joint pain, fever, nausea, dizziness, or local vaccine reaction, i.e., the main outcome measures. The event rate observed in a similar study recently published (near 63% of patient with reactogenicity outcome post vaccination, https://doi.org/10.1016/j.vaccine.2022.01.013), which is significantly higher than the one reported here (1.3%-7.8%), is consistent with thisobservation. This point should be discussed, as well as its impact on the interpretation possible of Table 2 (are Mild reaction really Mild since they are “significant”?)

Response:

You are correct. It is very likely that the format of the question in this study has led to an underestimation of mild symptoms. We have updated the Discussion to acknowledge the effect of question format and wording. Thank you for pointing out the very interesting comparable Dutch study which we have cited in that section.

“By defining an adverse event as a significant change in health and wellbeing in the online questionnaire (e.g. disruptive of usual activities), all events included in this analysis would likely be at least moderate according to severity grading scales commonly used in clinical research. In addition, the open question format did not prompt specific symptoms, which may reduce reporting of events that individual participants did not consider important or relevant. Therefore, we expect the rate of adverse events reported by our participants as mild to be lower than those reported in studies that did not use the same question format. For example, a Dutch web-based cohort study reporting data up to 13 days after vaccination asked participants to indicate if they had experienced specific common vaccine adverse reactions[13]. The Dutch study reported a far higher 62.9% overall rate of reactogenicity adverse events, similar to phase 3 vaccine trial findings.“

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Comment:

Bringing information on improvement of health / wellbeing in vaccine assessment is a good idea. However, an indicator on wellbeing deterioration could also have been beneficial, especially in the frame of a PASS. Combined with the previous comment, the absence of these indicator may give the impression that these questions are biased, and feed vaccine skepticism. I would recommend to justify this choice.

Response:

This question was added after discussion with patient grpoups, peer reviewers of the study protocol, public health colleagues and our ethics committee, in response to concerns about vaccine hesitancy prevalent in the UK at the time of study design. We agree that it could be intepreted as fuelling scepticism and have updated the Discussion to highlight the importance of considering the limitation of our approach.

“We were aware of media coverage of vaccine anxiety and concerns about vaccine hesitancy when designing our study. Most vaccine safety studies rightly concentrate on detecting negative symptoms. However, there was concern expressed amongst peers and public involvement group members that a study asking only about adverse consequences of vaccination could negatively impact vaccination rates. Our improved health and wellbeing finding is encouraging but should not be considered without acknowledging some limitations in our approach.”

Comment:

It takes some time to understand that patients may either register before or after vaccination.This point should be made clear in the method/participants section.

Response:

The methods/participation section has been updated accordingly.

Comment:

There are no exclusion criteria relative to the time to enroll after vaccination administration.This aspect may expose data collection to recall bias and also potentially to the over-registration of participant that experimented an outcome. If space allows, this point could be shortly discussed.

Response:

We have added the potential for recall bias and differential study enrollment to the Discussion, as follows:

“Participants were encouraged to join the study before receiving their first COVID-19 vaccination, but due to a fast UK vaccine roll-out and delays to study launch, many did not join until after their first vaccine. As a result, our findings may be subject to recall bias and the possibility that persons may have entered the study only to report an event that had already occurred.”

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Comment:

Description around how vaccine exposure is captured (batch, dates...) could be moved to the“Exposure” section.

Response:

This has been moved as advised.

Comment:

Text elaborating around Table 1 would be appreciated. A clear definition of the index date willhelp to better understand the content of the different categories.

Response:

Table 1 title and headings and explanatory footnotes have been adjusted to make clearer distinction between baseline characteristics and vaccine exposure. Additional footnote also added to explain "Other" category.

VERSION 2 – REVIEW

REVIEWER	Thurin, Nicolas Université de Bordeaux, Bordeaux PharmacoEpi
REVIEW RETURNED	03-May-2022

GENERAL COMMENTS	The paper has greatly improved in clarity and structure. Thank you

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